

REMARKS

Applicant notes that the Examiner has acknowledged that the Amendment filed March 27, 2003 has been received and entered. Upon entry of this Amendment, claims 35-41 and 50-61 and 65-67 are pending in the instant application. Claims 1-34 and 42-48 were previously cancelled, and claims 49 and 62-64 have been cancelled herein without prejudice or disclaimer. Applicant reserves the right to prosecute the cancelled subject matter, as well as the originally presented claims, in continuing applications. Claims 35-36, 39-40, 58-61 have been amended, and claims 65-67 have been added. Support for the claim amendments presented herein is found throughout the specification and in the claims as originally filed. For example, support for the method of enriching for liver stem cells recited by amended claim 35 is found at least at page 2, lines 15-22 and lines 27-35; at page 3, line 1 and lines 12-14; at page 4, line 33 through page 5, line 9; at page 6, lines 23-34; at page 7, lines 17-22; at page 9, lines 8-15; at page 12, line 19 through page 13, line 21; and in Figures 2, 3, 5A and 5B. Support for the amendment to dependent claim 36 is found at least at page 9, lines 8-15. Support for the amendments to dependent claims 39-40 is found at least at page 5, lines 3-5. Support for the method recited by amended dependent claim 61 is found at least at page at page 12, line 34 through page 13, line 13. Support for new claims 65 and 67 is found at least at page 2, lines 22-24 and lines 30-32; at page at page 6, lines 23-34; at page 7, lines 1-16; at page 13, lines 3-4; and in Figures 2, 3 and 4. Support for new claim 66 is found at least page 2, lines 19-22. Accordingly, no new matter has been added by these amendments.

I. Election/Restriction

Applicant notes that the Examiner has acknowledged that previously added claims 49-64, which depend directly or indirectly from elected claim 35, are encompassed by the elected invention. Applicant submits that new claims 65-67, which also depend directly or indirectly from claim 35, are also encompassed by the elected invention.

II. Priority

The Examiner has acknowledged that Applicant has complied with the requirements of 37 C.F.R. 1.78(a)(2) and (a)(5) for receiving the benefit of an earlier filing date, as “the

amendment to the first line of the specification reciting the priority information has perfected the priority claim.” (Office Action, page 2).

III. Oath/Declaration

The Examiner has indicated that the oath or declaration is defective due to non-initialed and/or non-dated alterations made to the oath or declaration.

Applicant submits herewith a Supplemental Combined Oath and Declaration in compliance with 37 C.F.R. 1.67(a). Applicant, therefore, requests that the Examiner withdraw this objection.

IV. Drawings

The Examiner has indicated that formal drawings will be required if the instant application is allowed. Applicant submits herewith formal drawings, Figures 1-5B, for this application. No new matter has been added in these Figures. Accordingly, Applicant requests that the Examiner replace the originally filed Figures 1-5B with the four sheets of formal drawings (Figures 1-5B) attached hereto.

V. Specification

The Examiner has acknowledged that the Abstract of the Disclosure filed on March 27, 2003 is in accordance with 37 C.F.R. 1.52(b)(4), and, consequently, the prior objection to the specification has been obviated.

VI. Claim rejections under 35 U.S.C. §112, second paragraph

Claims 35-41 and 49-64 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner has rejected claim 35 and its dependent claims as unclear, because claim 35 recites a method of obtaining “substantially pure liver stem cells”, but “the method as amended results in clusters of 2-5 cells not a pure population of liver stem cells.” In addition, the Examiner has asserted that the “sample of substantially pure liver stem cells” recited in claim 35 is unclear, because the specification defines “substantially pure” as “the *stem cell* or *doublets* are at least 60% of the cell population”, but “even if the composition is 100% doublets, then the greatest amount of stem cells would be 50% which would not fall under the definition of

‘substantially pure’ set forth in the disclosure.” Furthermore, the Examiner has also asserted that the method of claim 35 also appears “incomplete it is a method of obtaining pure liver stem cells, however only clusters of cells result from practicing the method.” (*See* Office Action, page 4).

Claim 35 has been amended herein to recite a method of enriching for liver stem cells by isolating a liver cell cluster from liver tissue to yield a population of clusters, wherein the liver cell cluster consists essentially of a total of two to five cells, at least one of which is a stem cell associated with a hepatocyte such that the stem cell includes an OV6 antigen, but lacks an OC2 antigen. According to the method of enriching recited by claim 35, the population of clusters is enriched for liver stem cells as compared to the liver tissue.

Thus, amended claim 35 is directed to a method of enriching for liver stem cells, rather than a method of obtaining a sample of substantially pure liver stem cells. As such, practicing the method of amended claim 35 results in a population of liver cell clusters that have been enriched for liver stem cells when compared to liver tissue. The claim has been further amended to recite that the total number of cells in the liver cell cluster is between two to five cells. In view of these amendments, Applicant, therefore, requests that the Examiner withdraw this rejection.

The Examiner has also rejected claim 36 has also been rejected under 35 U.S.C. § 112, second paragraph for being vague and unclear as to “how the recited method step is related to isolating liver stem cells as set forth in claim 35.” In particular, the Examiner has asserted that “it is unclear when, how or why periportal hepatocytes are isolated and how this is related to pure liver stem cells or isolation of the clusters.” (*See* Office Action, page 5).

Claim 36 has been amended to recite that the step of enriching for periportal hepatocytes associated with the biliary tree occurs prior to isolating the population of liver cell clusters from liver tissue. With regard to the Examiner’s comments that it is unclear why periportal hepatocytes are isolated, Applicant directs the Examiner’s attention to the specification at page 8, line 31 through page 9, line 15, which describes how enriching for periportal hepatocytes associated with the biliary tree is desirable because liver stem cells reside *in vivo* in a niche of the liver known as the canal of Hering. As is well known in the art, the canal of Hering is a biliary duct in the periportal region. Thus, the method recited by amended claim 36 enriches for periportal hepatocytes associated with the biliary tree before the liver cell clusters are isolated in

an effort to maximize the presence of liver stem cells in the enriched population of liver cell clusters. Thus, Applicant contends that amended claim 36 clearly and distinctly claims a method of further enriching for liver stem cells. Accordingly, Applicant requests that the Examiner withdraw this rejection.

The Examiner has also rejected claims 39-40 under 35 U.S.C. § 112, second paragraph for being vague and unclear as to “when the specific method steps are practiced in relationship to the method set forth in claim 35.” In addition, the Examiner has indicated that “claim 40 recites using the antigen OV6 which [is] required by the method of claim 35.” (*See Office Action*, page 5).

Claims 39 and 40 have been amended to address the Examiner’s remarks. As amended, claim 39 recites a method of enriching for liver stem cells in which the step of selecting for expression of desmoplakin occurs after the liver cell clusters have been isolated from liver tissue. Similarly, claim 40 has been amended to recite of enriching for liver stem cells in which the step of selecting for expression of the OV6 antigen recited in claim 35 occurs after the liver cell clusters have been isolated from liver tissue. Applicant, therefore, requests the withdrawal of this rejection.

The Examiner has also rejected claim 49 under 35 U.S.C. § 112, second paragraph as unclear and confusing because “it does not appear to further limit claim 35.” (*See Office Action*, page 5). Claim 49 has been cancelled. Thus, any rejection of this claim has been rendered moot and should be withdrawn.

Claims 58-60 have also been rejected under 35 U.S.C. § 112, second paragraph for lack of antecedent basis for the limitation “said sample.” Claims 58-60, which depend from independent claim 35, have been amended to replace all references to “said sample” with “said population of clusters,” as recited by amended claim 35. Accordingly, Applicant requests that the Examiner withdraw this rejection.

Finally, the Examiner has rejected claims 61-64 under 35 U.S.C. § 112, second paragraph as “confusing because removing the hepatocytes from the clusters should only leave stem cells wherein the population is 100% pure.” (*See Office Action*, page 6).

Claim 61 has been amended to recite a method of enriching for liver stem cells that include the step of dissociating the stem cell from the hepatocyte and removing the hepatocyte to

yield a sample of substantially pure liver stem cells. Claims 62-64 have been cancelled. Thus, withdrawal of this rejection is respectfully requested.

VII. Claim rejections under 35 U.S.C. §102

Applicant acknowledges that the Examiner has withdrawn the rejection of claims 35-38 under 35 U.S.C. § 102(b) as being anticipated by PCT Application WO 93/03142 by Reid *et al.*

VIII. Claim rejections under 35 U.S.C. §103

Applicant notes that the Examiner has withdrawn the rejection of claims 39-41 under 35 U.S.C. § 103(a) as being unpatentable over PCT Application WO 93/03142 by Reid *et al.* in view of Sell (Cancer Research, 1990) and Alison (Curr. Op. Cell Biol., 1996).

IX. Double Patenting

The Examiner has rejected claims 35-41 and 49-64 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 35-44 of U.S. Patent No. 6,129,911 ("the '911 patent").

Applicant submits herewith a terminal disclaimer over the '911 patent. Accordingly, Applicant requests that the Examiner withdraw this double-patenting rejection.

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CONCLUSION

On the basis of the foregoing amendments and the Examiner's acknowledgement that the claims are free of the art of record (Office Action, page 9), Applicant respectfully submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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Attachment:

--Formal Drawings (Figures 1-5B, four (4) sheets)

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